



Letter to the Editor

Why is lithium use declining?



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Dear Editors,

Bipolar Disorder (BD) is characterized by high morbidity and mortality, requiring life-long prophylaxis. Lithium was first introduced in the 1950s and has remained the gold standard medication for BD recommended in all international clinical practice guidelines, both for acute and maintenance therapy.

Despite robust evidence for lithium, its use is declining. Young and Hammond (2007) found that only 7.5% of BD patients in the US were prescribed lithium during initial phases of treatment, a markedly lower rate compared to England (Bastiampillai et al., 2017). Empirical studies in Canada, Switzerland, Germany, Austria and Denmark all demonstrated similar downward trends (Young and Hammond, 2007). However, despite the decline in worldwide lithium use, the prescription rates in regions like United Kingdom and Scandinavia remain high (Young and Hammond, 2007).

The complexity in the management of BD more often relates to long-term prophylaxis and prevention of relapse. Lithium has been shown to reduce the risk of manic relapse by 38% and depressive relapse by 28% (Geddes and Miklowitz, 2013). It has better evidence in control of both manic and depressive episodes when compared to valproate as a prophylactic agent (Geddes and Miklowitz, 2013). Evidence for long term use of antipsychotic medications as prophylactic agents is limited and marred by methodological flaws such as enrichment design and short duration of follow-up (Geddes and Miklowitz, 2013). Lithium is the only mood-stabilizing agent that not only has efficacy in bipolar depression but has also been shown to reduce the rate of hospitalization in unipolar depression (Tiihonn et al., 2017).

Patients with BD have a 6- to 10-fold risk of suicide compared to the general population (Sportiche et al., 2017) with approximately a third of BD patients attempting suicide at least once in their lifetime (Grande et al., 2017). Lithium is the only drug for BD that is demonstrated to have an anti-suicidal effect, with up to 50% reduction of suicide risk (Geddes and Miklowitz, 2013). It is therefore surprising that lithium prescription rates in the United States are declining despite rising rates of suicide since 1999 (Bastiampillai et al., 2017).

Lithium requires regular monitoring of plasma levels and renal and thyroid functions, unlike anticonvulsant mood stabilizers and second-generation antipsychotics. There are also several potential

contraindications to lithium prescription that are associated with BD. This includes substance abuse, medical comorbidities, as well as drug-drug interactions. Lithium also has other side-effects including weight gain, tremor, polydipsia, polyuria, dry mouth, thinning of the hair and sexual dysfunction, all of which are additional deterrents to lithium prescription.

One of the major limitations of lithium is its slow onset of action which makes it less favorable as monotherapy both in acute mania and acute depression (Malhi et al., 2009). As antipsychotics have a quicker onset of action, potentially more tolerable side-effect profile and are more efficacious against psychotic features (Fountoulakis et al., 2017), it is common for acute-phase antipsychotic medication to be continued long-term in the maintenance phase, instead of switching to lithium. However, the evidence to support this common clinical practice is weak.

The under-prescription of lithium can also be attributed to bias against lithium commercially. Pharmaceutically sponsored medications are favored in clinical trials funding (Malhi et al., 2009) and are more commercially profitable with a longer patent life, so more aggressive marketing is done in their favor (Young and Hammond, 2007). It is important to note that despite increasing published trials for newer agents, there is a lack of randomized controlled trial data on their efficacy in BD beyond 2 years (Lindström et al., 2017).

Lithium and clozapine are markedly alike; they both have clearly demonstrated long-term efficacy in multiple drug trials, reduce hospitalization rates, attenuate suicide rates with a drawback of significant side-effects (Verdoux et al., 2016). The authors therefore propose revisiting specialized-care pathways for lithium similar to clozapine pathways.

'Lithium clinics' first appeared in Western Medicine in the 1970s. Reinstating these specialty clinics would enable efficient lithium monitoring processes, improve psycho-education, optimize patient adherence and improve management of side-effects. The monitoring processes around lithium could replicate the clozapine coordination process, which improved clinical outcomes in the setting of treatment-resistant schizophrenia. Lithium use might also potentially increase in clinical practice with the establishment of such specialized clinics.

The clinical efficacy of lithium in BD is unparalleled given the large volume of evidence demonstrating its superior efficacy compared to

other alternative agents. The current worldwide decline in lithium use does not have a scientific basis and urgent systematic approach is required to reverse this concerning trend to improve the overall clinical and functional outcomes for BD patients. Lessons in particular should be learned from countries with relatively high prescription rates like Sweden and the United Kingdom to understand the systemic factors leading to their evidence-based use of lithium.

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Conflicts of interest

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